MEDICAL STAFF CONFERENCE

The Spectrum of Fungal Endocarditis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Dr. Sydney E. Salmon and Robert W. Schrier, Assistant Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, Ca. 94122.

DR. SMITH:* The case history of today's patient will be presented by Dr. Robert Carolan.

DR. CAROLAN:** This was the third University of California Hospital admission for this 51-year-old white man, a chemical engineer, whose complaints were fever and chills. At age 11 the patient was thought to have had rheumatic fever; however, at age 19 a diagnosis of ankylosing spondylitis was made. A murmur consistent with aortic insufficiency was discovered some time later and was felt to be related to the spondylitis.

Two years ago, the development of congestive heart failure necessitated replacement of the aortic valve with a Hufnagel prosthetic valve. The patient then did well until a month before this admission, when recurrent episodes of transient cerebrovascular ischemia and the development of a right lower quadrant visual field defect prompted his first admission here. Because he was felt to have recurrent emboli originating from the prosthetic valve, replacement of this device was advised. During his second admission the Hufnagel valve, which was found to have an adherent thrombus, was replaced with a valve fashioned with isologous fascia lata. During cardiopulmonary bypass, the patient received intravenous cephalothin prophylactically; no antibiotics were given subsequently. He remained afebrile and was discharged without a heart murmur.

Two days following discharge his private physician noted systolic and diastolic aortic valve murmurs during a follow-up physical examination. Blood cultures were sterile. Over the ensuing three weeks chills and high fever developed, finally prompting the present (third) admission.

On physical examination, the patient was acutely ill and obviously disabled by a poker spine. The rectal temperature was 39.8°C (103.6°F), pulse 130 beats per minute; respirations 22 per minute and blood pressure 130/70 mm of mercury. The neck veins were flat and the lungs were clear. There was a grade 5 of 6 aortic systolic ejection murmur and a grade 4 of 6 descrescendo diastolic murmur along the left sternal border. Petechiae and splinter hemorrhages were present. The spleen was not palpable.

Following the initial work-up, administration of aqueous penicillin was begun intravenously (40 million units per day), methicillin (15 grams per day initially; later 12 grams daily), and streptomycin (1 gram per day). The subsequent isolation of a species of flavobacterium from four blood cultures prompted discontinuance of all these antibiotics and the initiation of ampicil-

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lin therapy. The flavobacterium was sensitive to all antibiotics tested with the exception of cephalothin. On 12 grams of ampicillin per day, the patient's serum was bactericidal for the flavobacterium in a 1:8 dilution.

He felt better transiently, but fever and chills persisted and more petechiae developed on the mucous membranes. After 12 days of ampicillin therapy, sudden severe pain developed in the right leg with reduction of the pulses in that extremity. Two days later a right superficial femoral artery embolectomy was carried out and the excised clot contained a large mat of fungal material. Subsequent culture disclosed the presence of Aspergillus ustus. Amphotericin B was begun and cardiac operation was scheduled with a tentative diagnosis of aspergillus endocarditis. Two days before operation the aortic insufficiency murmur became greatly attenuated although congestive heart failure had not supervened.

At operation the aortic valve cusp was found to be perforated and there were large granular deposits on the undersurface of the valve and about the valve posts. Sponge pledges which had been used to approximate the apices of the cusps were also heavily involved in the same process. Histopathological examination revealed myriads of aspergillus organisms and subsequent cultures grew Aspergillus ustus. The fascia lata valve was replaced with a Wada-Cutter prosthetic valve.

The patient was maintained on amphotericin B following operation even though *in vitro* sensitivity studies indicated that the fungus was resistant to 10 μg per ml of amphotericin B. After two weeks the drug was discontinued because of deteriorating renal function and doubt that it was having any beneficial effect.

Over the next six weeks the patient had a number of episodes of hemorrhage from the right superficial femoral embolectomy site. A dacron graft was eventually required, but bleeding continued and when a thrombus formed at the site the graft had to be removed. Culture of the excised graft and numerous cultures of blood, sputum and urine were sterile. The patient was discharged, after a total of 78 days in the hospital, on chronic anticoagulation therapy.

Four days later he was admitted for the fourth time with rectal bleeding. No bleeding focus could be found on examination of the gastrointestinal tract, but anticoagulation was discontinued. During the week in hospital he was continously febrile. Six blood cultures were negative and no new murmurs were noted. Once again he was discharged.

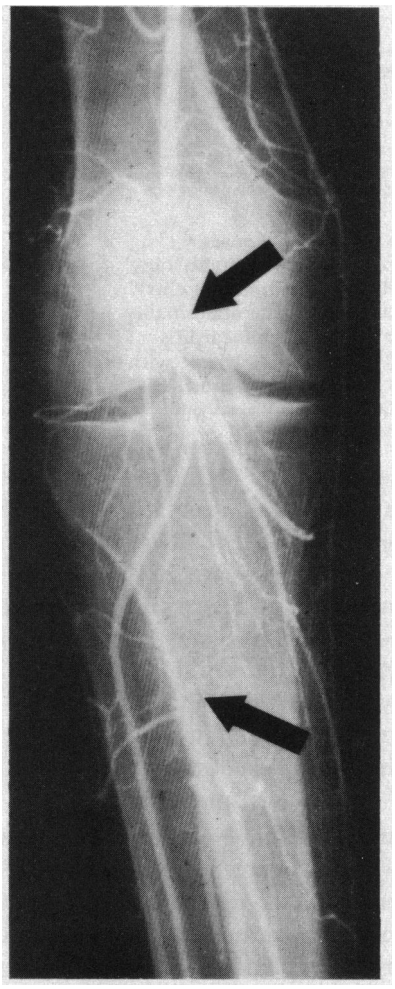

Figure 1.—Arteriogram demonstrating obstruction of the popliteal artery. The upper arrow points to the site of arterial obstruction by the embolus. The lower arrow indicates the distal segment of the obstructed vessel. Collateral circulation about the upper tibia is apparent.

Five days later the patient died suddenly at home. At autopsy performed at U.C. Medical Center, numerous large clumps of vegetation were seen about the aortic valve ring and the prosthetic device. These contained myriads of aspergillus organisms. There were no metastatic foci of infection.

DR. SMITH: May we now see the x-ray films?

RADIOLOGIST: On the chest x-ray film the day before replacement of the fascia lata valve with the Wada valve, cardiomegaly and decided

TABLE 1.—Predisposing Factors and Responsible Organisms in Fungal Endocarditis

Predisposing Factors	*Responsible Fungi*
A. Disseminated Myotic Infection	Histoplasma capsulatum (rarely Aspergillus species, Blastomyces dermatitidis, Candida albicans, Coccidioides immitis, Cryptococcus neoformans and Phycomyces species)
B. Intravenous Narcotic Abuse (Heroin; Paregoric)	Candida species (including albicans, guilliermondii, parapsilosis, and stellatoidea)
C. Impaired Host Defenses 1. Prolonged antibiotic therapy 2. Intravascular portal of entry 3. Cardiac valvular abnormality a) Bacterial endocarditis b) Open heart surgery, with or without valve prosthesis	Candida species most frequently Aspergillus species increasingly common (rarely Histoplasma capsulatum, Torulopsis glabrata, and Paccilomyces species)

prominence of the ascending aorta were noted. Two days after valve replacement, cardiomegaly persists, there is a left lower lobe infiltrate, and several chest tubes are in place. Subsequently the heart diminished in size. The arteriogram done before embolectomy (Figure 1) shows an obstruction in the popliteal artery with considerable collateral circulation below the point of occlusion. The spine films demonstrate the "bamboo spine" and fused sacroiliac joints characteristic of ankylosing spondylitis.

DR. SMITH: We have chosen this morning not to discuss this patient's primary illness of ankylosing spondylitis, or its association with aortic insufficiency, but rather the occurrence of fungal endocarditis which was a complication of the operation for aortic valve incompetence. Dr. David Drutz of the Division of Infectious Diseases will discuss this patient's illness.

DR. DRUTZ:* Thank you, Dr. Smith. Although I plan to devote most of this morning's discussion to fungal endocarditis, it is important to note that this patient had bacterial endocarditis before aspergillus infection supervened. It is not widely appreciated that bacterial endocarditis and its treatment, or overtreatment, are among the factors predisposing to fungal endocarditis. The fact that a species of flavobacterium was the original infecting microorganism is of particular interest. These Gram-negative bacilli are not normal inhabitants of the bowel, but occur naturally in soil and water. There have been several instances of infection with flavobacterium following cardiovascular operation,[1] and flavobacterium endocarditis has been reported.[2] The potential role of flavobacteria in Gram-negative pneumonias following the use of contaminated nebulizer equipment has also been emphasized.[3] It is intriguing that this patient received prophylactic cephalothin therapy, because the flavobacter species subsequently isolated from his blood was sensitive to every antibiotic tested with the exception of cephalothin. Thus, although it is difficult to be certain of the portal of entry of the flavobacterium, the micoorganism may well have been selected out by prophylactic antibiotic therapy.

Factors Predisposing to Fungal Endocarditis

Among the microbial agents capable of initiating endocarditis, fungi rank rather low. As shown in Table 1, there are three distinct settings in which fungal endocarditis tends to occur.

Disseminated Mycotic Infection. North American blastomycosis, coccidioidomycosis, cryptococcosis, aspergillosis, and mucormycosis have all been complicated by endocarditis on rare occasion.[4] Valve involvement is generally only one feature of widespread infection and is usually unsuspected during life. Less unusual is the occurrence of endocarditis in histoplasmosis; at least 18 such cases have been reported.[5-8] Although clinical findings of endocarditis may be prominent in these patients, Histoplasma capsulatum is difficult to isolate from the blood. Thus the diagnosis of histoplasmosis usually depends on isolation of fungi from other organs. It is of interest that meningitis, a particularly rare manifestation of histoplasmosis, has occurred in association with histoplasma endocarditis on at least five occasions.[7,9] Although endocarditis may occur as one feature of disseminated candidiasis, this appears to be rare.[10] More often candida

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endocarditis appears "to be the result of initial implantation of the organism on the heart valves, with subsequent hematogenous disseminated fungal infection."[4]

Intravenous Narcotic Abuse. Endocarditis is a well-recognized complication of intravenous heroin and paregoric abuse. We have seen cases following the use of amphetamines ("speed") intravenously. Fungi are relatively rare among the microorganisms causing endocarditis in addicts.[11] Nevertheless, fungal endocarditis does appear to occur in higher incidence in heroin addicts than in the general population.[12] In the absence of underlying valvular disease, such infections tend to involve the aortic valve. Fungi do not appear to share the propensity of staphylococci to invade the right side of the heart.[13]

It is not clear why narcotic addicts are particularly prone to endocarditis. Presumably the repeated injection of contaminated drugs through dirty skin with dirty needles produces frequent bacteremia or fungemia. Nevertheless, reticuloendothelial mechanisms are normally highly efficent in sterilizing the blood. It is possible that the drugs also damage the heart valves in some as yet undefined manner.

Candida species (albicans, guilliermondii, parapsilosis, stellatoidea) have been responsible for virtually all reported cases of fungal endocarditis in narcotic addicts. Indeed, aspergillus endocarditis did not develop in one addict who was known to have repeatedly injected himself with cocaine heavily contaminated with Aspergillus niger.[13]

Impaired Host Defenses. Three factors in particular appear to hamper host defense against fungi and to predispose to fungal endocarditis: prolonged antibiotic therapy, intravascular portal of entry, and cardiac valvular abnormality.

• Prolonged Antibiotic Therapy: Alterations in normal bacterial flora attendant upon prolonged antibiotic use are well known. When there is underlying cardiac valvular disease, and particularly when a portal for entry of fungi into the bloodstream is provided, fungal endocarditis may result.

• Intravascular Portal of Entry: Any breach in the integrity of cutaneous or mucosal surfaces provides a portal whereby fungi may gain access to the circulation. Prolonged intravenous therapy provides direct access to the bloodstream from the skin, and fungemia, particularly candidemia, has become a particularly common problem with the use of plastic intravascular cannulas for drug administration and hyperalimentation. Fungi are not the only microorganisms to invade the bloodstream in this situation, but antibiotic therapy tends to select them out. While candidemia can often be terminated by simple removal of the contaminated cannula,[14] disseminated candidiasis may develop. In the presence of underlying valvular disease, endocarditis may result.

Cooper and his colleagues have investigated the roles of antibiotic therapy and valvular damage in fungal endocarditis.[15] In their study, aortic insufficiency was produced surgically in 12 of 14 dogs. All animals subsequently received 3.2 x 10^7 Candida guilliermondii intravenously. Nine dogs with aortic insufficiency then received eight days of antimicrobial therapy—penicillin and streptomycin for five of the animals and tetracycline for four. At autopsy, three of the dogs which had received penicillin and streptomycin and one of those treated with tetracycline had candida endocarditis. Endocarditis did not develop in the two dogs with intact aortic valves or the three with aortic insufficiency but no antibiotic therapy.

• Cardiac Valvular Abnormality: The development of fungal endocarditis during the course of prolonged intravenous antibiotic therapy for bacterial endocarditis is a well-documented[16] but generally unappreciated phenomenon. Candida species are the usual superinfecting microorganisms. We recently had a patient in who Torulopsis glabrata endocarditis developed during the course of penicillin and streptomycin therapy for enterococcal endocarditis. In the present patient, it is not clear whether flavobacter and aspergillus endocarditis coexisted from the outset, or the aspergillus invaded a valve previously infected with flavobacteria.

Fungal endocarditis is a well-recognized complication of valvulotomy procedures and an increasingly common complication of prosthetic valve replacement. Prophylactic antibiotic therapy is generally employed during such surgical procedures and it is likely that fungi are selected out in this way.

Although candida species are most frequently responsible for fungal endocarditis in these circumstances,[17,18] aspergillus species are an increasingly frequent cause of infection.[19-22] In-

deed, up to 1957 there were reports of only four cases of aspergillus endocarditis in the literature.[4] Histoplasma capsulatum has invaded a prosthetic valve on one occasion,[7] and species of Paecilomyces have been implicated in two infections.[23] The present case has a particularly intriguing parallel in the literature. Mershon and his coworkers[24] described a patient with flavobacter endocarditis involving a fascia lata graft in a previously damaged posterior mitral valve leaflet. The patient died despite therapy with multiple antibiotics. At autopsy, Aspergillus terreus was present as a huge mass arising from the posterior mitral leaflet, and disseminated abscesses were present in nearly every organ. However, secondary foci of infection do not commonly develop when fungi invade a prosthetic valve.[25]

There is no evidence that any particular prosthetic appliance is uniquely susceptible to fungal invasion. Infections have occurred on fascia lata grafts,[24] homografts,[26] Hufnagel valves[21] and Starr-Edwards valves,[20] among others.

Clinical Features

The clinical features of fungal endocarditis generally mirror those of bacterial endocarditis. Even focal glomerular lesions have been reported.[27] Three points, however, bear particular emphasis.

Blood Cultures. When species of candida are the infecting agent, blood cultures are generally positive.[4] In contrast, other fungi are rarely isolated from the blood, even when they are specifically sought. Indeed, the clinical manifestations highly suggestive of endocarditis in the absence of positive blood cultures should raise the possibility of fungal growth.[4]

Continuous bacteremia is an important feature of bacterial endocarditis; it reflects the continuous shedding of microorganisms into the bloodstream from an infected endothelial surface.[28] The reason that blood cultures are not consistently positive for fungi is not clear, but this phenomenon may reflect inadequacy of present culture techniques or the presence of extremely low titers of fungi in the blood. Approximately 10^2 bacteria are present per ml of blood in bacterial endocarditis;[28,29] similar data are not available for fungal endocarditis. The importance of culturing large volumes of cerebrospinal fluid when attempting to establish the diagnosis of

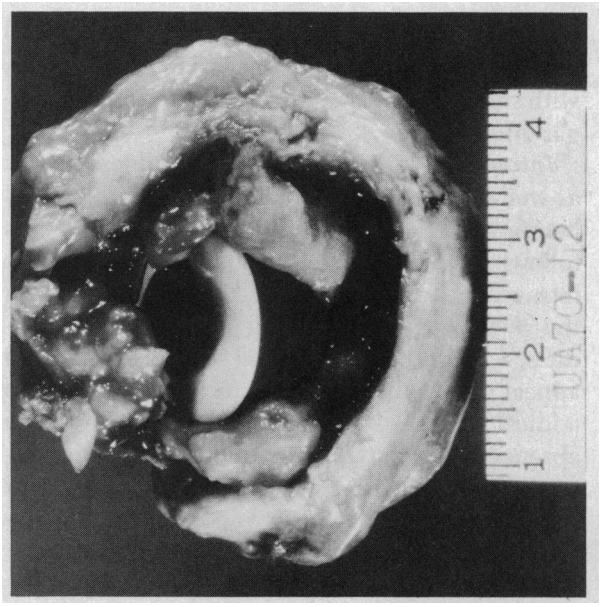

Figure 2.—Autopsy specimen of the excised aortic valve ring. For purposes of illustration, the prosthetic valve has been moved from its correct position. Large clumps of vegetation are apparent along the circumference of the valve ring.

fungal meningitis has been emphasized.[30] Perhaps a similar approach is indicated for the blood culture in fungal endocarditis. Akbarian[31] has demonstrated the irregularity of positive blood cultures in experimental histoplasma endocarditis in dogs. Incisions 4 mm long were made in the aortic valve cusps of five dogs. Afterward 5×10^7 yeast-phase H. capsulatum injections were given intravenously and all the dogs developed endocarditis followed by widespread dissemination and elevation of histoplasma complement fixation titers. Of three dogs in which blood cultures were followed serially, one had only 3 of 37 and another only 5 of 35 positive blood cultures. The third dog had 10 of 22 cultures positive including nine positive in a row (a situation more reminiscent of bacterial infection). These cultures were obtained over a period of five to eight weeks.

Major Artery Emboli. No other feature of fungal endocarditis is so suggestive of this form of infection as a tendency for development of embolic occlusions of large arteries.[4,5,17,18,32] Fungal vegetations on heart valves tend to become very large. The verrucae are soft and easily detached, producing large emboli. Figure 2 shows the size of the aspergillus vegetations on the aortic valve at autopsy in the case we are discussing today.

The importance of major embolic phenomena

cannot be overemphasized because surgical removal, pathologic examination and culture of embolic material can establish the diagnosis of fungal endocarditis. Both aspergillus[33] and histoplasma[5] endocarditis have been diagnosed during life by excision and examination of an embolus from a large, accessible artery. Embolectomy in these circumstances is a diagnostic rather than a therapeutic procedure. Thus excision is warranted even though the embolus may pose no threat to the blood supply.

Changing Heart Murmurs. This is generally an overstated criterion for the diagnosis of endocarditis. A dramatic change in a preexisting murmur or the sudden development of a new murmur generally signals perforation of a valve cusp, rupture of chordae tendineae, or some other catastrophe. One does not await a change in a murmur before accepting a diagnosis of endocarditis.

In fungal endocarditis, changing murmurs may reflect the sheer bulk of vegetative mass at the valve orifice. In the patient we are discussing today, the disappearance of a previously obvious aortic insufficiency murmur before operation suggested partial occlusion of the aortic valve orifice in the absence of a lowered cardiac output from congestive heart failure.

Treatment

The role of antifungal chemotherapy is severely limited in fungal endocarditis. While histoplasma,[8] cryptococcus[34] and candida[35] endocarditis have been cured with amphotericin B alone, it has become abundantly clear that valve excision is required in the vast majority of cases. When a prosthetic valve is infected, operation offers the only hope of cure—and even that hope is slim. Even though the aspergillus endocarditis of the present patient was diagnosed during life, the administration of amphotericin B and the prompt excision of the infected valve only extended his life for a few weeks. Ultimately aspergillus infection disrupted the new prosthetic valve. Nevertheless, although the prognosis for fungal endocarditis appears to be very poor, cure may be possible if diagnosis is established early, appropriate antifungal therapy is begun, and appropriate surgical measures are undertaken.[36]

DR. SMITH: Thank you, Dr. Drutz. We will take time for one or two questions.

DR. HOPPER:* Do these patients present without fever?

DR. DRUTZ: The literature indicates that fever is a fairly regular manifestation of fungal endocarditis.[37]

DR. MURRAY:† The big fungus problem in California is coccidioidomycosis. At least from clinical evidence this fungus is generally felt to be relatively resistant to amphotericin. I wonder if you have any sensitivity data about it that could provide guides for treatment.

DR. DRUTZ: Dr. Murray is referring to data which we have published concerning the amphotericin sensitivity of a variety of pathogenic fungi. A scheme for the therapy of systemic mycotic infections was based on this information in conjunction with serial measurements of the amphotericin serum concentration.[38] Basically, patients should receive amphotericin B in sufficient daily dosage to maintain serum levels of two times the minimal inhibitory concentration (MIC) of the infecting fungus. The strains of Histoplasma capsulatum, Blastomyces dermatitidis, and Cryptococcus neoformans were sensitive to between 0.098 and 0.780 micrograms of amphotericin B per ml. We were able to maintain postinfusion amphotericin serum levels at least twice the MIC of these fungi with approximately half the daily dosage at present recommended (that is, 0.5 mg per kg of body weight per day, against the recommended 1.0 to 1.5 mg per kg per day). Treatment was conducted for an arbitrary period of ten weeks. The study indicated that the daily dose of amphotericin need not be increased to the point of frank toxicity before therapeutic response can be expected.

This approach has been tried in only one patient with coccidioidomycosis. We recently treated an elderly woman with a C. immitis paravertebral abscess by means of this method. The infecting fungus was sensitive to less than 0.5 mcg of amphotericin per ml. Published data on C. immitis indicates that its amphotericin sensitivity pattern is similar to that of H. capsulatum, with MIC's ranging from 0.5 to 1.0 mcg per ml.[39]

I need not emphasize the dangers to the laboratory worker of manipulating C. immitis. At present there is no practical way for the routine

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hospital laboratory to measure the amphotericin sensitivity of coccidioides strains. Further, it is not clear whether a lowered dosage regimen would be feasible in patients with disseminated coccidioidomycosis, since these patients may respond poorly even with doses of amphotericin to the maximum of tolerance. However, the patient with the paravertebral abscess has done extremely well though never receiving more than 25 mg of amphotericin a day.

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